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Prevalence of anti-tissue transglutaminase antibodies in apparently healthy Saudi general populations

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ABSTRACT

Objectives: To determine the prevalence of anti-tissue transglutaminase antibodies in apparently healthy general populations in the Kingdom of Saudi Arabia. *Subjects and Methods*: This cross-sectional study was conducted at the King Abdulaziz University in the period 13 May 2019 – 1 October 2019. We used blood samples in ethylene diamine tetra acetic acid (EDTA) tubes, taken from 714 healthy blood donors, consisting of 622 Saudi (311 males) and 92 non-Saudi (46 males). The anti-tissue Transglutaminase-IgA (tTG-

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IgA), was determined in the plasma using ELISA kits (Euroimmun Medical Laboratory Diagnostics, Seekamp, Luebeck, Germany). The ABO and Rh blood groups were determined by the slide agglutination method using antisera from *Dialab GmbH – Neudor, Austria*. For the data analysis we used the statistical package for social science (IBM SPSS Inc., version 20). *Results*: 1-tTG-IgA in Saudi normal subjects. Eighteen (2.9%) plasma samples were positive for tTG-IgA antibodies. Positive males were twice as much as positive females, with no significant difference (p=0.151). Positivity for tTG-IgA also showed no significant correlations (p>0.05) neither with the blood groups (ABO and Rh) nor with the age groups. 2- tTG-IgA in non-Saudi normal subjects. Three (3.2%) samples were positive for tTG-IgA, with no significant difference between Saudi and non-Saudi subjects (P>0.05). *Conclusion*: High prevalence of tTG-IgA in apparently healthy blood donors suggesting a high prevalence of undiagnosed celiac disease in the Saudi population. Males were double the rate of females for the tTG-IgA positivity.

Keywords: tTG-IgA in SA, tTG-IgA in general population, tTG-IgA in blood donors, prevalence of tTG-IgA.

1. INTRODUCTION

Celiac disease (CD) is an autoimmune disorder that affects genetically predisposed individuals in response to gluten ingestion (Fasano, 2012). In addition to the gluten-dependent symptoms, diagnosis of CD depends on the CD-specific antibody levels and the histological changes in the duodenal biopsy (Klapp et al., 2013). The global pooled antibodies-proven prevalence (seroprevalence) of CD is 1.4% (Singh et al., 2018); whereas the biopsy-proven prevalence is 0.58% (Biagi et al., 2010), and 0.7% (Singh et al., 2018). CD is also common in the Arab population (Abu-Zekry et al., 2008; Ben Hariz et al., 2007; Bdioui F et al., 2006). In Saudi Arabia, the pooled seroprevalence of CD is 2.7% (Safi, 2018), representing the fixed event rate (by meta-analysis) of the four different concerned studies in Saudi Arabia (Khayyat, 2012; Al-Hussaini, et al., 2017; Aljebreen et al., 2013; Al Hatlani, 2015). Three of these studies involved school-aged students (children and adolescents) with a CD seroprevalence of 2.2-3%, which was higher in females than in males (Al-Hussaini, et al., 2017; Aljebreen, et al., 2013; Al Hatlani, 2015), whereas one study (Khayyat, 2012) involved adult normal subjects (204 blood donors), but with lower seroprevalence (1.5%), which was higher in males than in females. Thus, the aim of our current study was to evaluate the CD seroprevalence (using IgA anti-tTG) among a larger cohort (622) of adult Saudi blood donors with its relation to gender, age groups and blood groups.

2. SUBJECTS AND METHODS

This cross-sectional study was conducted at king Abdulaziz University in the period 13 May 2019 – 1 October 2019, following the approval of the Research Committee / Biomedical Ethics Unit, KAU (Reference No 309-19). This study included seven hundred and fourteen healthy blood donors that included six hundred and twenty-two Saudis and ninety-two of none-Saudi nationality. At time of blood donation, all blood donors provided a written consent of no objection for using their blood in research or for any other required purpose. We used blood samples in ethylene diamine tetra acetic acid (EDTA) tubes that were tested negative for HCV, HBV and HIV by the molecular diagnostic laboratory at KAUH. The blood samples had been labeled by specific codes that were assigned by the blood bank at KAUH. We used these codes to obtain some data from the donors' files in the blood bank that included age, gender and nationality for each blood donor. Plasma was separated from all EDTA blood samples, divided into two aliquots and stored at –75 °C until required. The anti-tissue Transglutaminase-IgA (tTG-IgA) was determined in the plasma using ELISA kits (Euroimmun Medical Laboratory Diagnostics, Seekamp, Luebeck, Germany). Samples with tTG-IgA value >20 unit/ml were considered positive according to the manufacturer's instructions. All positive samples were reconfirmed using the same type of kit. The ABO and Rh blood groups were determined, in the whole blood, by the slide agglutination method using monoclonal antisera from *Dialab GmbH – Neudor, Austria*. For the data analysis we used the Statistical Package for Social Science (IBM SPSS Inc., version 20). Chi-square tests were used to compare proportional data. A Pearson's correlation was used to determine the bivariate relationship. A non-parametric Mann-Whitney U test was used for categorical variables. A *P* value less than 0.05 was considered statistically significant. The results were illustrated as tables, diagrams and figures.

3. RESULTS

Selection and characterization of cohorts

During a period of five months (13 May 2019 – 1O October 2019), 4951 EDTA blood samples were obtained that involved 61 non-Saudi females and 311 Saudi females (Fig 1). All of the 311 (100%) Saudi females' samples were used in this study, in addition to an

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equal number (311) of males' samples that were randomly selected to be age-matching with the females. Among the 61 (100%) non-Saudi females, we selected those nationalities containing more than four females; thus 46 none-Saudi females were used in this study, in addition to an equal number (46) of non-Saudi males' samples that were randomly selected to be matching with the females for age and nationality. Thus, the total cohort involved 622 Saudi plasma samples and 92 non-Saudi plasma samples. The demographic and baseline characteristics of the Saudi and none-Saudi cohorts involved are shown in Table 1. Males and females numbers were equal within the Saudi and the non-Saudi groups with no significant difference between genders among each group ($p>0.05$) (Table 2).

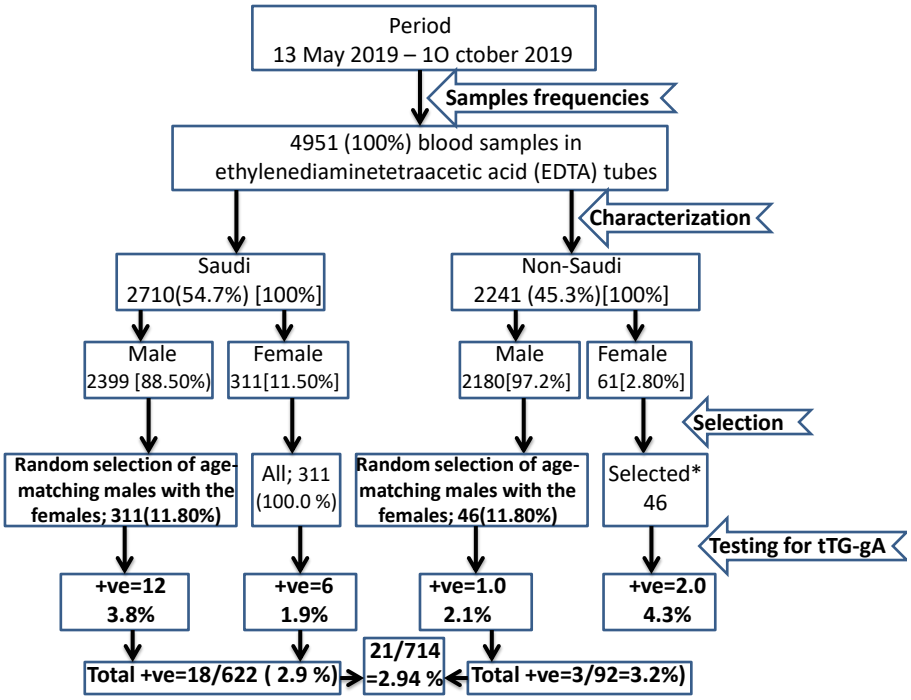

Figure 1 PRISMA flow-diagram showing the overall process of the study. *Among the 61 non-Saudi females, we selected the nationalities containing more than 4 females.

Table 1 Demographic and basic characteristics of the cohort of the study.

Category	Variable	Mean (SD) or Number (%)
Non- Saudi cohort	Number	92
	Age	32.7 years (SD 10.34)
	Age range	17-59 years
	Gender (F/M)	46/46 (1/1)
	Rh +ve	90 (97.8%)
	O blood group	46(50%)
	A blood group	17(18.5%)
	B blood group	26((28.3%)
	AB blood group	3 (3.3%)
	tTG-IgA +ve	3 (3.2 %)
	tTG-IgA value	>154.7 U/ml (SD>78.5 U/ml)**
	TTG-IgA value range	65 - >200 U/ml**
	Number	622

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Saudi cohort	Age	26.36 years (SD 8.22)
	Age range	17-58 years
	Gender (F/M)	311/311 (1/1)
	tTG-IgA +ve	18 (2.9%)
	TTG-IgA value	>108.1 U/ml (SD >64.3 U/ml)*
	tTG-IgA range	23 - >200 U/ml*
Age groups of the Saudi cohort	1-19 years	60 (9.6%)
	20-29 years	419 (67.4%)
	30-39 years	83(13.3%9)
	40-49 years	50 (8.9%)
	5-59 years	10 (1.6%)
Blood groups of the Saudi cohort	0	307 (49.5%)
	A	192 (30.9%)
	B	97 (15.6%)
	AB	26 (4.2%)
	Rh+ve	568(91.3%)
	Total	(100%)

*Four samples showed tTG-IgA values >200 U/ml, three with values >100, Eight with values > 50 U/ml, two with values > 40 U/ml and one with 23 U/ml; all result were confirmed by retesting. ** Two samples showed tTG-IgA values >200 U/ml and one with a value of 65 U/ml.

Table 2 Saudi and non-Saudi genders among the cohort of the study

		Gender		Total	P*	P*
		Male	Female			
Saudi	Count	311	311	622		
	% within saudi	50.0%	50.0%	100.0%		
	% within Gender	87.1%	87.1%	87.1%		
	% of Total	43.6%	43.6%	87.1%		
	Age mean/years(SD)	26.36(8.2)	26.36(8.2)	26.36(8.2)	0.88**	
	Age range/year	17-58	17-58	17-58		
None-Saudi	Count	46	46	92		
	% within saudi	50.0%	50.0%	100.0%		
	% within Gender	12.9%	12.9%	12.9%		
	% of Total	6.4%	6.4%	12.9%		
	Age mean/years(SD)	33.1(10.6)	32.2(10.1)	32.7(10.3)	0.7**	
	Age range/year	17-59	17-57	17-59		
Total	Count	357	357	714		
	% within saudi	50.0%	50.0%	100.0%		
	% within Gender	100.0%	100.0%	100.0%		0.00
	% of Total	50.0%	50.0%	100.0%		

* Mann-Whitney U test **p>0.05

Results concerning tTG-IgA in the Saudi cohort

A total number of 622 [311 male (50%)] Saudi plasma samples were tested for tTG-IgA and for blood grouping. Eighteen (2.9%) samples showed positive results for tTG-IgA antibodies that were double in males (12 males and 6 females), with no significant correlation between tTG-IgA positivity and gender (P=0.15) (Table 3 and Figure 2). All of the 18 positive tTG-IgA reactors were

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Rh+ve (100%), eight (44.4%) were O (Rh+ve), eight (44.4%) were A(Rh+ve), two (11.1%) were AB (Rh+ve) and none were B blood group; with no significant correlation neither between tTG-IgA positivity and the ABO blood groups (P=0.1) nor between tTG-IgA positivity and the Rh blood group (P=0.185) (Table 3). Within each blood group, tTG-IgA positivity was at a maximum in the AB blood group (2/26=7.7%) followed by A blood group (8/192=4.2%) then O blood group (8/307=2.6%) and none for the B blood group (Table 3 and Figure 3).

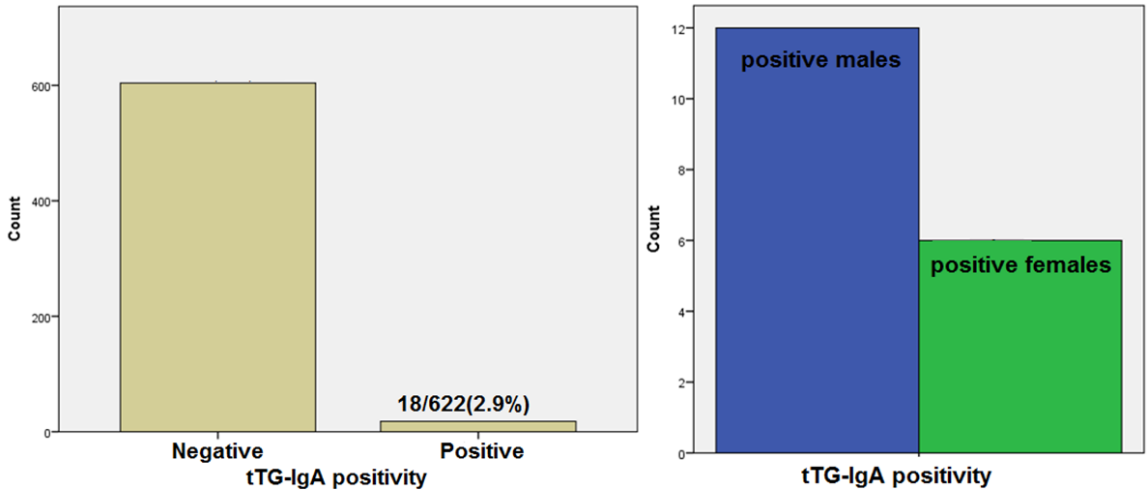

Fig 2. tTG-IgA positivity within the cohort and within gender.

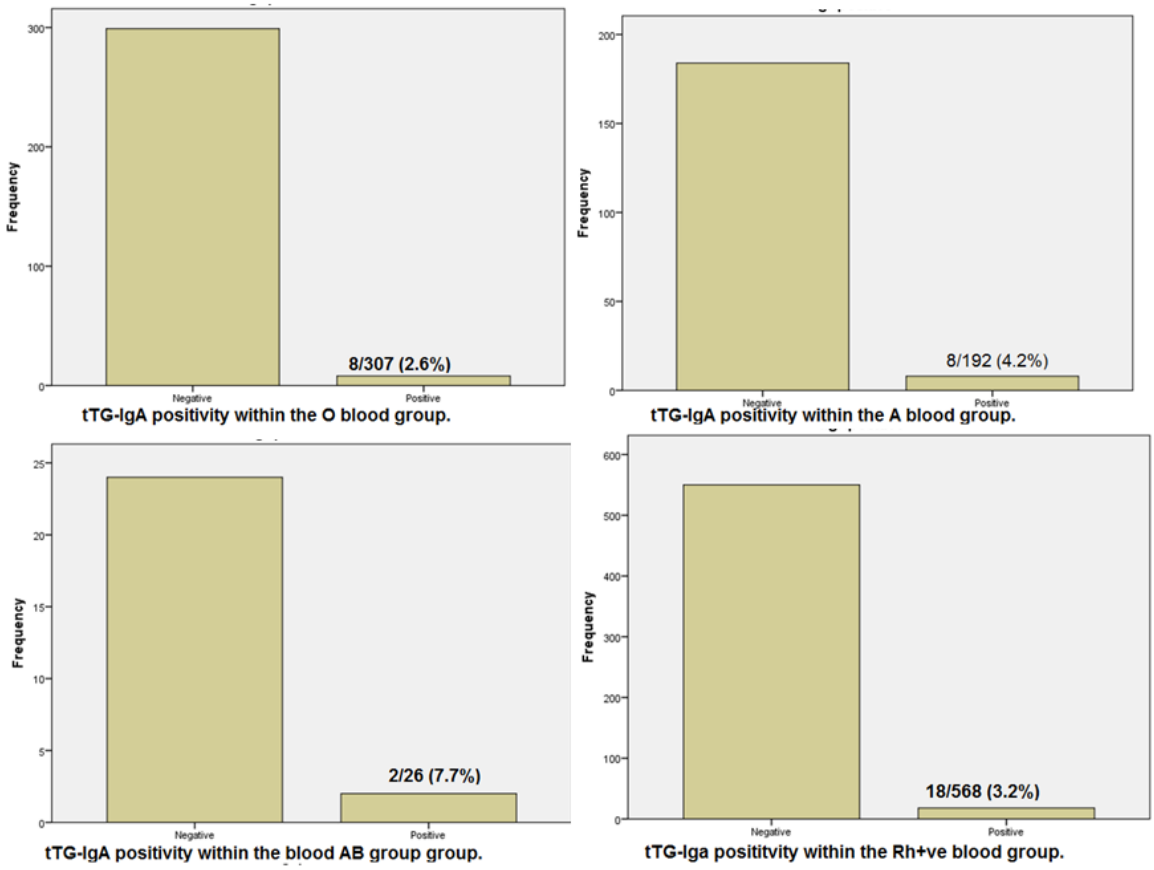

Figure 3 tTG-IgA positivity within each blood group group.* * tTG-IgA positivity wase zero in the B blood group and The Rh^{-ve} blood group.

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Table 3 Demographic variables in relation to tTG-IgA

Variable	Negative tTG-gA N (% within each group) [% within tTG-IgA positivity]	Positive tTG-IgA N (% within each group) [% within tTG-IgA positivity]	Total N (% within each group) [% within tTG-IgA positivity]	Correlation significance	Strength of association
Saudi					
Yes	604 (97.1%)	18 (2.89%)	622 (100%)	X^2 =0.038; DF=1; P=0.846*	Phi= 0.007 Cramer's V=0.007
No	88 (98.9%)	3 (3.2%)	92 (100.0%)		
Total	693 (97.06%)	21 (2.94%)	714 (100%)		
Saudi gender					
Male	299 (96.1%) [49.5%]	12 (3.9%) [66.7%]	311 (100.0%) [50.0%]	X^2 =2.0; DF=1; P=0.15*	Phi= -0.058 Cramer's V=0.058
Female	305 (98.1%) [50.5%]	6 (1.9%) [33.3%]	311 (100.0%) [50.0%]		
Total	604 (97.1%) [100.0%]	18 (2.9%) [100.0%]	311 (100.0%) [100.00%]		
Saudi age groups/Year					
1-19	59 (98.3%) [9.8%]	1 (1.7%) [5.6%]	60 (100.0%) [9.6%]	X^2 =2.04; DF=4; P=0.728*	Phi= -0.057 Cramer's V=0.057
20-29	408 (97.4%) [67.5%]	11 (2.6%) [61.1%]	419 (100.0%) [67.4%]		
30-39	79 (95.2%) [13.1%]	4 (4.8%) [22.2%]	83 (100.0%) [13.3%]		
40-49	48 (96.0%) [7.9%]	2 (4.0%) [11.1%]	50 (100.0%) [8.0%]		
50-59	10 (100.0%) [1.7%]	0,0 (0.0%) [0.0%]	10 (100.0%) [1.6%]		
Total	604 (97.1%) [100.0%]	18 (2.9%) [100.0%]	622 [100.0%] [100.0%]		
Saudi blood groups					
O	299 (97.4%) [49.5%]	8 (2.6%) [44.4%]	307 (100.0%) [49.4%]	X^2 =6.2; DF=3; P=0.1*	Phi= 0.1 Cramer's V=0.1
A	184 (95.8%) [30.5%]	8 (4.2%) [44.4%]	192 (100.0%) [30.9%]		
B	97 (100.0%) [16.1%]	0 (0.0%) [0.0%]	97 (100.0%) [15.6%]		
AB	24 (92.3%) [4.0%]	2 (7.7%) [11.1%]	26 (100.0%) [4.2%]		
Total	604 (97.1%) [100.0%]	18 (2.9%) [100.0%]	622 (100.0%) [100.0%]		

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Saudi Rh blood group					
Negative	54 (100.0%) [8.9%]	0.0 (0.0%) [0.00	54 (100.0%) [8.7%]		
Positive	550 (96.8%) [91.1%]	18 (3.2%) [100.0%]	568 (100.0%) [91.3%}	X^2 =1.76; DF=1; P=0.185*	Phi= 0.53 Cramer's V=0.53
Total	604 (97.1%) [100.0%]	18 (2.9%) (100.0%)	622 (100.0%) [100.0%]		

tTG : tissue transglutaminase; DF: Degrees of freedom; *p>0.05

The 18 positive tTG-IgA (100%) reactors were distributed between age groups as follows: 11 (61.1%) in 20-29 years, four (22.2%) in 30-39 years, two (11.1%) in the 40-49 years and one (5.6%) was <20 years, while none were in the >50 years group; with no significant correlation between tTG-IgA positivity and the age groups (P=0.728). On the other hand, within each age group, tTG-IgA positivity was maximum in 30-39 years (4/83=4.8%), then 40-49 Years (2/50= 4%), then 20-29 years (11/419 = 2.6%, then 1-20 yers (1/60 =1.7%), and 00.00% (/00.00/10) for 50-59 years (Table 3 and Figure 4).

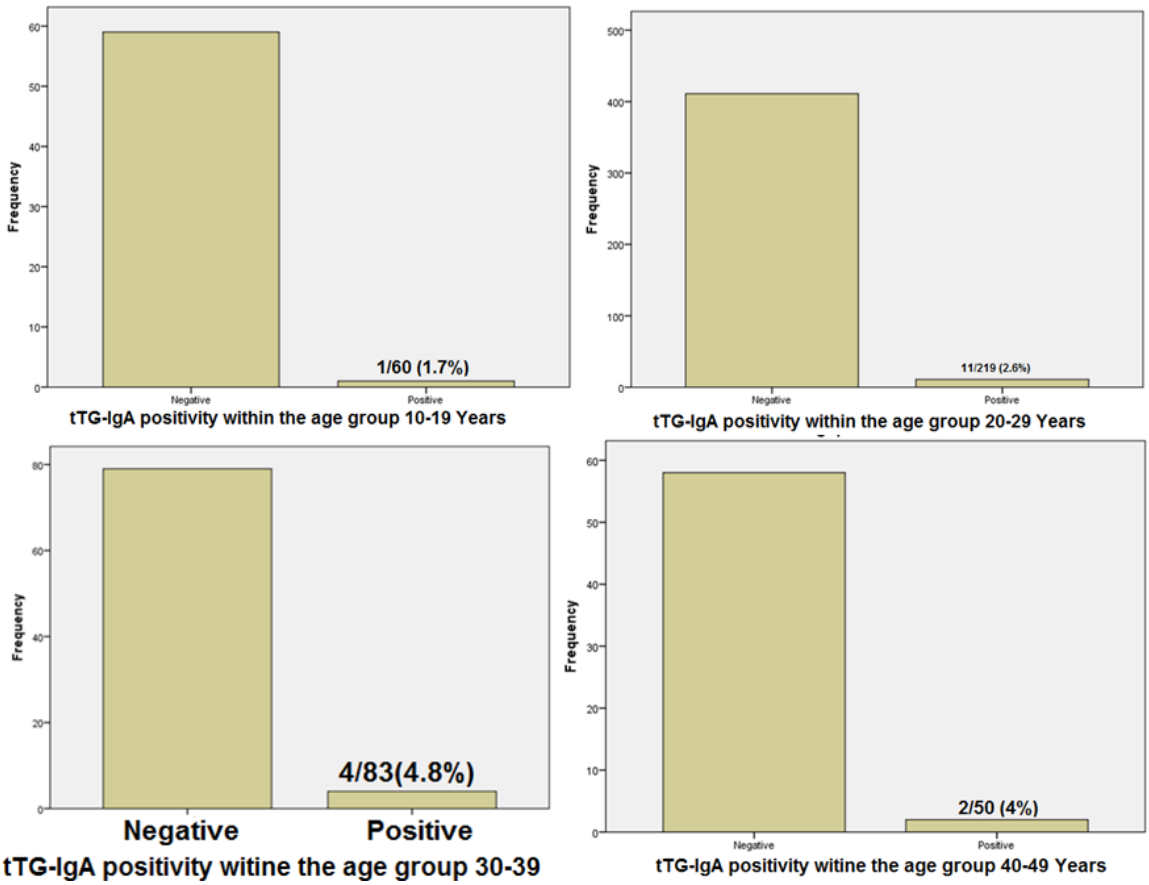

Figure 4 tTG-IgA positivity within each age group.* * tTG-IgA positivity wase zero in the age group 50-59Years.

Table 4 A Pearson's correlation between tTG-IgA positivity and different variables (gender, ABO blood groups, Rh blood group and age groups) among the 622 normal Saudi blood donors.

		Age group	Blood groups	Rh groups	Gender
tTG-IgA positivity	Pearson Correlation	0.031	0.006	0.053	-.058
	P value	0.44*	0.875*	0.185*	.152*
	N	622	622	622	622

*p>0.05

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A Pearson's correlation was also performed to determine the relationship between tTG-IgA positivity and each of the following independent vasriables: gender, blood groups, Rh groups and age groups, among the 622 normal populations (Table 4). tTG-IgA positivity showed no correlation neither with gender (r = -0.058, N=622, p=0.152), ABO blood groups (r = 0.006, N=622, p=0.875), Rh blood group (r = 0.053, N=622, p=0.185), nor age groups (r = 0.03, N=622, p=0.44).

Results concerning the non-Saudi cohort

The non-Saudi cohort involved 92 subjects, from five different nationalities; these being three Arabs [Yemeni 30(32.5%), Egyptian 12(13.0%), and Palestinian 12(13.0%)] and two non-Arabs (Philippino 26(28.2%) and Indians 12(13.0%)). The numbers of females and males were equal in each nationality. Three (3.2%) samples were positive for tTG-IgA, with no significant correlation (Pearson's correlation: -0.038; p: 0.316) between nationalities and tTG-IgA positivity (Table 5).

Table 5 Positivity tTG-IgA among the non-Saudi cohort of the study according to their nationalities

	Nationalities that were selected for serology*					Total	Nationalities that were not selected for serology**	Total
	Yamani	Egyptian	Palestinian	Pilipino	Indian			
Count (%) of non-Saudi females in the cohort	15 (32.6%)	6 (13.0%)	6 (13.0%)	13 (28.2%)	6 (13.0%)	46 (100%) [75.5%]	15 {24.5%]	61 [100%]
Count (%) of non-Saudi males selected matching with females	15 (32.6%)	6 (13.0%)	6 (13.0%)	13 (28.2%)	6 (13.0%)	46 (100%) [75.5%]		
Count (%) of the selected non-Saudi subjects	30 (32.6%)	12 (13.0%)	12 (13.0%)	26 (28.2%)	12 (13.0%)	92 (100%) [75.5%]		
tTG-IgA positivity %	1 1.1%	1 1.1%	Negative 0.00%	1 1.1%	Negative (0.00%	3/92 (3.2%)		
Pearson's correlation (p value)	-0.038 (0.316)							

*Nationality with females' number > 4 were selected for tTG-IgA serology ** Nationality with females ≤ 4 were not selected for tTG-IgA serology; which included: Syrian, Jordanian, Pakistani, Bangladeshi, Djibouti, Chadian, Sudanese, Eritrean, Chinese and Kenyan.

4. DISCUSSION

Celiac disease (CD) is an autoimmune enteropathy that requires gluten ingestion to affect individuals who are genetically susceptible (Fasano et al., 2012). It was not until the last decade of the last century when it became obvious that CD is not a rare condition (Biagi et al., 2010), but is rather a common disorder in Europe, both North and South Americas, Australia, North Africa, the Middle East and in South Asia (Accomando et al., 2004). Concerning the CD-seroprevalence in the kingdom of Saudi Arabia, there have been only four different studies; three of them (Al-Hussaini et al., 2017; Aljebreen et al., 2013; Al Hatlani, 2015) involved large cohorts (1141 - 7930) of school-aged students (children and adolescents), with CD seroprevalence of 2.2-3% which was higher in females than in males. However, the fourth study (Khayyat, 2012) differs in that it involved apparently normal adult subjects, different geographical area (the western region) of KSA and lower CD seroprevalence (1.5%), which was higher in males than in females. These disparities stimulated us to perform this study that involved 622 adult Saudi blood donors in which the male and females were matched, not only in number (311 each) but also age wise; in order to evaluate the CD seroprevalence using tTG-IgA and its relation to gender, age groups and blood groups.

In this study, we present a CD seroprevalence of 2.9%, which was estimated among supposedly healthy Saudi blood donors aged 17 to 58 years. This seroprevalence (2.9%) was closely similar to that reported by Al-Hussaini et al. (2017) (2.78%) and by Al Hatlani (2015) (3%), who both used school-aged students within different regions in the KSA. On the other hand, our reported

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seroprevalence (2.9%) was almost twice the prevalence (1.5%) reported by Khayyat (2012) who conducted his study within the same region of our study (the western region of the KSA), within the same group of subjects (adult blood donors), using the same serological method (tTG-IgA), but we used three times larger cohort in which the females and males were matching in frequency (311 each) and age. Interestingly, our results also found a higher prevalence in males versus females, opposite to findings that have been published in the KSA (Al-Hussaini, et al., 2017, Aljebreen, et al., 2013, Al Hatlani, 2015) and globally (Singh et al., 2018) that CD is more common in females than in males. Moreover, our study was conducted seven years after the study of Khayyat (2012) suggesting an increase in CD-seroprevalence over time, a conclusion which was also drawn by the meta-analysis of Singh (2018). Globally, our result (2.9%) was twice as high as the global seroprevalence (1.4%) reported by the meta-analysis of Singh (2018), and 3.6 times higher than the seroprevalence (0.8%) in the USA (Katz et al., 2011) in health-care subjects aged ≥ 18 years. In comparison with the reported international CD-seroprevalence, among adult blood donors, using the same serological method (tTG-IgA), our results (2.9%) was markedly higher than the CD-seroprevalence in Brazil (Alencar et al., 2012; Pereira et al., 2006) (0.6% and 0.28%), 0.5% in Spain (García Novo et al., 2012), 0.86% in Iran (Bahari et al., 2010), 0.55% in India (Kochhar et al., 2012), 0.21% in Tunisia (Bdioui et al., 2012). This was also higher than the seroprevalence (0.73%) reported in the Akureyri region of Iceland (Johannsson et al., 2009) among adult and children blood donors using the same serological method we used (tTG-IgA).

We used the tTG-IgA testing due to its high sensitivity (98%), and high specificity (98%) and its availability as ELISA, whereas EMA (95% sensitivity and 99% specificity) and ARA (72% sensitivity and 99% specificity) both possess inter-observer variability because they are both immunofluorescence that requires individual reading of each sample under a fluorescent microscope (Leffler and Schuppan, 2010; Nandiwada and Tebo, 2013; Parizade et al., 2009). On the other hand, the AGA test was abandoned for routine diagnosis as it also existed in healthy individuals and in non-celiac enteropathies (Hill et al., 2005). A new promising test was introduced for the detection of deamidated gliadin peptide Abs (DGPAs) (Schwertz et al., 2004), particularly for children below seven years old and/or for IgA-immuno compromised patients (Barbato et al., 2012; Mozo et al., 2012), and a recent electrochemical immunosensor for DGPAs was described, as an alternative to the ELISA kits (Neves et al., 2013).

We found that the rate of tTG-IgA was lower in those of blood groups O (2.6%) or A (4.2%) than in those of blood group AB (7.7%) (mean relative incidence 0.33: 1 and 0.55:1, respectively) with no significant correlation (P >0.05) between tTG-IgA positivity and blood groups. There was no study concerning the relation between CD and blood groups in the Saudi population (Safi, 2018). In the UK, Langman et al. (1969) demonstrated a slightly lower incidence of the CD disease in those of blood groups O or B than in those of blood group A, which was related to chance (P >0.05) but not to a genetic predisposition association. In this respect, we are in concordance with these findings. It was in the middle of the last century when the association between blood group A and gastric cancer was reported by Aird et al. (1953). Studies concerning associations between ABO blood groups and GIT diseases included also the association between blood group A and salivary tumors (Cameron, 1958; Osborne and De George, 1962), and gastric cancer (McConnell, 1966); and the association between blood group O with duodenal and gastric ulcers (Aird et al., 1954; Clarke et al., 1955).

We found that the rate of tTG-IgA was at a maximum in those of age group 30-39 years (4/83=4.8%), then 40-49 Years (2/50= 4%), then 20-29 years (11/419 =2.6%, then 1-20 yers (1/60 =1.7%), and zero (00.00/10) for 50-59 years; with no significant correlation (P >0.5) between tTG-IgA positivity and age groups.

One limitation in this study is that it does not include testing for the total IgA, the absence of which may have produced false-negative results in our study. However, the common rate of IgA deficiency is 0.15-0.2%, and 2%–3% in those with CD (Kumar et al., 2002), thus the seroprevalence in our study (2.9%) could had been slightly higher (2.98%) if we excluded the expected IgA deficient subjects (up to 3% = 12 subjects). Furthermore, no IgA-deficient individual was detected in the Saudi blood donors (Khayyat, 2012). The strengths of this study are that (1) we used a large sample size of 622 samples, which were double that are needed to be included to determine the prevalence in the Middle East (Khayyat, 2012). (2) the study involved matched male and female subjects in both number and age (3) we used plasma samples that were proven to be free of HIV, HBV and HCV that may cause false–seropositivity (Kurien et al., 2012), (4) we used a non-Saudi group that showed higher female positivity than male positivity.

5. CONCLUSION

High prevalence of tTG-IgA in apparently healthy blood donors suggesting a high prevalence of undiagnosed celiac disease in the Saudi population. Males were double the rate of females for the tTG-IgA positivity. Suggestion for further work. The results of the study justify the evaluation of MHC-DQ2 and –DQ8 in both male and female of apparently healthy Saudi blood donors.

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Disclosures

The current study was not funded or supported by any drug company. This paper is unique, is not under consideration by any other publication and has not been published elsewhere.

Ethical approval

The study was approved by the Research Committee / Biomedical Ethics Unit, KAU (Reference No 309-19).

Conflicts of Interest

The author declares that he has no conflicts of interest.

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